REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-8 are in this case. Claims 1-8 have been rejected. Claims 2 and 7 have now been canceled. Claims 1, 3-6 and 8 have now been amended.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 1-8 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 2 and 7 have now been cancelled. Claims 1, 3-6 and 8 have now been amended.

The Examiner states that the scope of the claim is broad, the working example does not demonstrate the claimed method, the effect of ASF and the outcome of treatment are unpredictable and the teachings in the specification are limited. Therefore, the Examiner concludes, that it is necessary to have additional guidance and to carry out further experimentation to assess the effects of ASF in treating various diseases resulting from aberrant splicing in cells.

In order to expedite prosecution of this case, Applicant has elected to limit the subject matter of claims 1, 3-6 and 8, to treatment of cystic fibrosis. Thus Amended claim 1 now recites treatment of cystic fibrosis by use of "an alternative splicing factor (ASF) capable of at least partially correcting aberrant splicing of a transcript of a CTFR gene".

While reducing the present invention to practice, Applicants demonstrated accurate "normal" splicing of affected CFTR gene products by co-transfection of COS cells with recombinant exogenous splicing factors (Example 4), and correction of aberrant splicing of CFTR transcripts in cells of cystic fibrosis patients by expression of recombinant exogenous splicing factors (Example 5). Thus, Applicants have provided evidence that the underlying genetic pathology of cystic fibrosis can be corrected using ASFs.

In addition to this experimental evidence which clearly supports treatment of CF with an ASF, the instant specification and the state of the art prior at the time of filing of the instant application clearly provide one of ordinary skill in the art with the motivation and guidance necessary to treat (in-vivo) cystic fibrosis through the use of an ASF capable of correcting aberrant splicing of a CTFR RNA.

CF is a severe autosomal recessive disease caused by well characterized mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. As is demonstrated by the results presented in the instant specification, aberrant splicing resulting from such mutations can be at least partially corrected by Alternative Splicing Factors (ASFs). ASFs, which participate in creating protein diversity, have been intensely studied in the last decade and as a result, information as to the function and site of action of these factors is widely available.

Since the mutations underlying CF are well characterized and since the general function of various ASFs is also known or described in the instant application, it is Applicants strong opinion that one of ordinary skill in the art would have no difficulties in selecting or identifying ASFs that are capable of carrying out the aforementioned function, namely to at least partially correct CTFR splicing.

With respect to the experimental data provided in the instant application, Applicant would like to point out that in-vitro results which clearly demonstrate correction of the sole causative agent of CF by demonstrating CTFR gain-of-function are highly predictive of an in-vivo effect due to the low complexity of CF etiology. Thus, contrary to disorders which are caused by complex interactions between several biological components in which in-vitro results are not always predictive of an in-vivo outcome, the present case presents a simple one gene - one effect relationship in which mutations of a known and quantifiable gene lead to a well characterized effect. In such cases, strong correlation between in-vitro data and in-vivo results is expected.

The fact that in-vitro results can predict treatment is demonstrated by a recently reported study on splicing correction in familial dysautonomia. Familial dysautonomia (FD) is an autosomal recessive neurodegenerative disorder caused by a T to C transition in a donor splice site of the IKBKAP transcript. An article published by Anderson et al. in 2003 [EGCG corrects aberrant splicing of IKAP mRNA in cells from patients with familial dysautonomia, Biochem Biophys Res Commun. 2003 Oct 17; 310(2):627-33)] demonstrated that regulation of an ASF (namely hnRNP) promoted production of a functional gene product and led the researchers to conclude that such regulation offers a "therapeutic modality for individuals with FD".

With respect to treating conditions, Applicant disagrees with the Examiner in that the specification does not provide sufficient support. Although the instant specification does not provide the exact amounts of an ASF necessary for treatment, such mere "calibration" cannot be considered trial and error experimentation since a therapeutically effective amount can be easily determined by an ordinary skilled artisan privileged to the teachings of the present invention, especially in light of the fact that the effect of an ASF on CTFR splicing is easily quantifiable using standard molecular techniques (e.g. PCR).

In addition, the instant application clearly teaches administration (page 5 line 26 to page 6 line 25) by, for example, having the ASF "administered directly to the cells ... within a carrier suitable for inhaling and penetrating the lungs" (page 6 lines 6-9 of the instant specification).

Or by using an "expression vector ... attached to targeting moiety, such as, for example, a suitable antibody or a ligand of a specific receptor which can specifically bind to the membranes of the desired cells and thus the expression vector to the desired cell population, or to the organ or tissue comprising said cell population. In such a case, the expression vector may be administered systemically, and the targeting moiety ensures that it reaches its proper target cell population" (page 6 lines 10-16 of the instant specification).

Thus, Applicant strongly believes that the in-vitro results and detailed description clearly provide the enablement and written description support necessary

for making and using the present invention without having to resort to trial and error experimentation.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 1-8 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiners rejections are respectfully traversed. Claims 2 and 7 have now been canceled, rendering moot the Examiner's rejection. Claims 1, 3-6 and 8 have now been amended.

With respect to claim 1 (and claims 2-8) the Examiner points out that these claims are indefinite as to what effect the ASF has in treatment. Claim 1 has now been amended to include "thereby treating cystic fibrosis in said individual" in the last line of this claim. With respect to claim 7, the Examiner states that this claim does not further limit claim 1 from which it depends. Claim 7 has now been cancelled thereby rendering moot the Examiner's rejection with respect to this claim.

In view of the above amendments and remarks it is respectfully submitted that claims 1, 3-6 and 8 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Enc.:
One-month extension fee
Anderson et al.